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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,760	07/09/2003	Harry V. Gelboin	015280-389200US	2288
20350 7590 07/26/2007 TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834			EXAMINER SKELDING, ZACHARY S	
			ART UNIT 1644	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/616,760

Applicant(s)

GELBOIN ET AL.

Examiner

Zachary Skelding

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 19 March 2007.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 13-15, 18-22, 24-26 and 74-82 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 75 is/are allowed.
- 6) ☒ Claim(s) 13-15, 18-22, 24-26, 74 and 76-82 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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### DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 19, 2007 has been entered.
2. Applicant's amendment to the claims filed March 19, 2007 has been entered.

Claims 13-15, 25 and 26 have been amended.

Claims 1-12, 16-17, 23 and 27-73 have been canceled.

Claims 76-82 have been added.

Claims 13-15, 18-22, 24-26 and 74-82 are pending.

3. **Claims** 13-15, 18-22, 24-26 and 74-82 **are under consideration** as they read on a monoclonal antibody that competes with MAb 763-15-5 for specific binding to p450 2C9 allelic variants 2C9\*1, 2C9\*2, and 2C9\*3.

The rejections of record can be found in the previous Office Action, mailed January 17, 2007.

This Office Action is in response to Applicant's amendment filed March 19, 2007.

The previous rejection under 35 U.S.C. § 112, 1<sup>st</sup> paragraph has been withdrawn in view of applicant's amendment to the claims.

The previous rejection under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph has been withdrawn in view of applicant's amendment to the claims.

New Grounds of Rejection are set forth below.

4. Claim 79 is objected to because of the following informalities: it is duplicative with claim 78. Appropriate correction is required.
5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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6. Claims 13-15, 18-22, 24-26, 74, 77 and 80-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

**This is a New Grounds of Rejection.**

**A. Phenanthrene metabolism by at least 50%: Claims 13-15, 18-22, 24-26, 74, 77 and 81.**

Claim 13, and dependent claims thereof, recite “wherein the MAb 763-15-5 inhibits *2C9\*1* catalyzed metabolism of phenanthrene *by at least 50%* and *2C9\*2* catalyzed metabolism of phenanthrene *by at least 50%...*”

Claim 77 recites, “the competitive antibody of claim 76 that “inhibits *2C9* catalyzed metabolism of phenanthrene *by at least 50%*”

Claim 81 recites, “the competitive antibody of claim 76 that “inhibits *2C9\*1* catalyzed metabolism of phenanthrene *by at least 50%* and *2C9\*2* catalyzed metabolism of phenanthrene *by at least 50%...*”

Applicant points to Figure 2 and pages 6, lines 2-25 and page 26, lines 4-12 in support of this claim.

However, the disclosure at page 26 does not mention the 763-15-5 antibody so it does not support the claim.

While Figure 2 and the disclosure on page 6 are directed to the 763-15-5 antibody, they do not explicitly disclose the limitation “wherein the MAb 763-15-5 inhibits *2C9\*1* catalyzed metabolism of phenanthrene by at least 50% and *2C9\*2* catalyzed metabolism of phenanthrene by at least 50%”, much less an antibody that competes with the 763-15-5 antibody for specific binding to the human cytochrome p450 2C9 allelic variants *2C9\*1*, *2C9\*2* and *2C9\*3* as recited in base claim 76 and has the particular ability to “inhibit *2C9\*1* catalyzed metabolism of phenanthrene *by at least 50%* and *2C9\*2* catalyzed metabolism of phenanthrene *by at least 50%...*” as recited in claim 81.

Moreover, while other parts of the instant specification not pointed to by applicant, such as page 4, 2<sup>nd</sup> paragraph, disclose antibodies that compete with 763-15-5 and specifically inhibit *2C* catalyzed metabolism of phenanthrene by at least 50%, the instant application does not provide blazemarks nor direction for claims to a competitive antibody that “inhibits *2C9* catalyzed metabolism of phenanthrene *by at least 50%*”.

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Furthermore, according to the instant specification at the paragraph bridging pages 9-10, Mab 763-15-5 inhibits 2C9\*1 and 2C9\*2 catalyzed metabolism of phenanthrene by more than 85 and 90%, respectively. So it is unclear how MAb 763-15-5, *per se*, could inhibit 2C9\*1 and 2C9\*2 catalyzed metabolism of phenanthrene by *at least 50%*.

Thus, the instant specification does not provide sufficient blazemarks nor direction for the limitation “wherein the MAb 763-15-5 inhibits 2C9\*1 catalyzed metabolism of phenanthrene by at least 50% and 2C9\*2 catalyzed metabolism of phenanthrene by at least 50%” or for an antibody that competes with Mab 763-15-5 which has these particular properties or which “inhibits 2C9 catalyzed metabolism of phenanthrene *by at least 50%*”.

These limitations, which were not clearly disclosed in the specification as-filed, change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

A generic or a sub-generic disclosure cannot support a species unless the species is specifically described.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Applicant is required to cancel the new matter in the response to this Office action.

Alternatively, applicant is invited to provide sufficient written support for the limitations indicated above.

See MPEP 714.02 and 2163.06.

#### **B. Phenanthrene metabolism by at least 70%: Claim 25**

Claim 25 is directed to the competitive antibody of claim 13 that “inhibits the phenanthrene metabolism...of...P450 allelic variant 2C9\*1 by at least 70% and inhibits the phenanthrene metabolism...of...P450 allelic variant 2C9\*2 by at least 70%.”

Applicant points to Figure 2 and pages 6, lines 2-25 and page 26, lines 4-12 in support of this claim.

However, the disclosure at page 26 does not mention the 763-15-5 antibody so it does not support the claim.

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While Figure 2 and the disclosure on page 6 are directed to the 763-15-5 antibody they do not explicitly disclose inhibition of “phenanthrene metabolism...of...P450 allelic variant 2C9\*1 by at least 70% and inhibits the phenanthrene metabolism...of...P450 allelic variant 2C9\*2 by at least 70%” by the 763-15-5 antibody, much less an antibody that competes with the 763-15-5 antibody for specific binding to the human cytochrome p450 2C9 allelic variants 2C9\*1, 2C9\*2 and 2C9\*3 as recited in base claim 25 and has the ability to “inhibit the phenanthrene metabolism...of...P450 allelic variant 2C9\*1 by at least 70% and inhibit the phenanthrene metabolism...of...P450 allelic variant 2C9\*2 by at least 70%.”.

Thus, the instant specification does not provide blazemarks nor direction for the competitive antibody of claim 13 that “inhibits the phenanthrene metabolism...of...P450 allelic variant 2C9\*1 by at least 70% and inhibits the phenanthrene metabolism...of...P450 allelic variant 2C9\*2 by at least 70%.”.

This limitation, which was not clearly disclosed in the specification as-filed, changes the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

A generic or a sub-generic disclosure cannot support a species unless the species is specifically described.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Applicant is required to cancel the new matter in the response to this Office action.

Alternatively, applicant is invited to provide sufficient written support for the limitations indicated above.

See MPEP 714.02 and 2163.06.

### **C. Diclofenac metabolism by at least 50%: Claims 80 and 82**

Claim 80 recites the competitive antibody of claim 76 that “inhibits 2C9 catalyzed metabolism of diclofenac by at least 50%.”

Claim 82 recites the competitive antibody of claim 76 that “inhibits 2C9\*1 catalyzed metabolism of diclofenac by at least 50%, inhibits 2C9\*2 catalyzed metabolism of diclofenac by at least 50%,...”

Applicant points to Figures 9 and 10 and pages 7, lines 9-12 and page 27, lines 6-20 in support of these claims.

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While the Figures and disclosure cited by applicant are directed to the ability of the 763-15-5 antibody to inhibit diclofenac metabolism, they do not explicitly disclose antibodies that compete with the 763-15-5 antibody for specific binding to the human cytochrome p450 2C9 allelic variants 2C9\*1, 2C9\*2 and 2C9\*3 as recited in base claim 76 and have the ability to “inhibit 2C9 catalyzed metabolism of diclofenac by at least 50%.” or “inhibit 2C9\*1 catalyzed metabolism of diclofenac by at least 50%, inhibits 2C9\*2 catalyzed metabolism of diclofenac by at least 50%,...”.

Thus, the instant specification does not provide blazemarks nor direction for the competitive antibody of claim 76 that “inhibits 2C9 catalyzed metabolism of diclofenac by at least 50%.” or “inhibits 2C9\*1 catalyzed metabolism of diclofenac by at least 50%, inhibits 2C9\*2 catalyzed metabolism of diclofenac by at least 50%,...”.

These limitations, which were not clearly disclosed in the specification as-filed, changes the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

A generic or a sub-generic disclosure cannot support a species unless the species is specifically described.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Applicant is required to cancel the new matter in the response to this Office action.

Alternatively, applicant is invited to provide sufficient written support for the limitations indicated above.

See MPEP 714.02 and 2163.06.

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7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 13-15, 19-21, 25, 76, 77, 80, 81 and 82 are rejected under 35 U.S.C. 102(b) as anticipated by Mei et al. (WO 01/011035 A1), as evidenced by Kimura et al. (Nucleic Acids Res. 1987 Dec 10;15(23):10053-4) and the instant specification at page 2 which discloses that the 2C9\*2 allele has Cys144, and as further evidenced by Wester et al. (J. Biol. Chem. 2004 Aug 20;279(34):35630-7), Lewis et al. (Curr. Med. Chem. 2006;13(22):2645-52), Miners et al. (Br J Clin Pharmacol. 1998 Jun;45(6):525-38, of record) and Harlow et al. (Antibodies, Cold Spring Harbor Press, pp. 23-35 (1988)).

As a preliminary matter, it should further be noted that according to the instant specification, “competing antibodies” include antibodies binding to the same epitope as a reference antibody and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to the human cytochrome P450 2C family member by at least 10, 25, 50 or 75%. See instant specification, page 11, last paragraph.

Thus, claims 13, 76, and dependent claims thereof, given their broadest reasonable interpretation consistent with the specification, read on everything from a competitive antibody that binds an epitope different from the 763-15-5 antibody but nonetheless sterically competes with the 763-15-5 antibody for its specific binding to the human cytochrome p450 2C9 allelic variants by at least 10%, to a competitive antibody that binds the same or nearly the same epitope as the 763-15-5 antibody and competes with the 763-15-5 antibody for its specific binding to the human cytochrome p450 2C9 allelic variants by at least 75%.

It should further be noted that claims 13, 76, and dependent claims thereof, given their broadest reasonable interpretation consistent with the specification, will be considered as reading on a monoclonal antibody that competes with monoclonal antibody MAb 763-15-5 for its (MAb 763-15-5's) specific binding to all three “human cytochrome p450 2C9 allelic variants 2C9\*1, 2C9\*2 and 2C9\*3”.

However, the competitive antibodies of claims 13, 76, and dependent claims thereof, while competitive with monoclonal antibody MAb 763-15-5 for its specific binding to 2C9\*1, 2C9\*2 and 2C9\*3, do not themselves necessarily specifically bind only to the human cytochrome p450 2C9 allelic variants 2C9\*1, 2C9\*2 and 2C9\*3, i.e., the competitor antibody could also specifically bind other p450 enzymes, such as 2C8.



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With this claim construction in mind, Mei teaches murine monoclonal anti-2C9 p450 antibodies raised against microsomes expressing the polypeptide encoded by the 2C9 cDNA described by Kimura et al. (Nucleic Acids Res. 1987 Dec 10;15(23):10053-4), and eukaryotic cell lines producing said antibodies (see entire document, in particular, page 5, last paragraph to page 6, Example 2, pages 15-17 and Example 14 on pages 27-28).

As evidenced by Kimura Figure 1, the 2C9 cDNA used to make the Mei antibodies has Cys 144, which means that it encodes the 2C9\*2 allele as evidenced by the instant specification at page 2. Mei further teaches the characterization of two particular anti-2C9\*2 antibodies, "30-12-1" and "73-19-2", which inhibit 2C9\*2 catalyzed metabolism of flurbiprofen and bind 2C8 and 2C9\*2 in an immunoblot (see entire document, in particular, page 13, 3<sup>rd</sup> paragraph to page 14; Figures 13, 14 and 16 and pages 9 and 10 explanation of Figures 13 and 14).

While it is noted that the antibodies of Mei likely bind an epitope that is different from the epitope bound by the 763-15-5 antibody given the abilities of the Mei antibodies to bind both 2C8 and 2C9\*2, one of ordinary skill in the art would nonetheless immediately recognize that the antibodies of Mei will inherently "compete" with 763-15-5 for its specific binding to 2C9\*1, 2C9\*2 and 2C9\*3 (see below how the claimed competitive antibodies are being interpreted in light of the disclosure of the instant specification) as evidenced by the teachings of Wester, Lewis, Miners and Harlow.

More particularly, given that the 73-19-2 antibody inhibits 2C9\*2 metabolism of flurbiprofen as taught by Mei,

and

further given, as evidenced by Wester, the structure of 2C9 p450 bound to flurbiprofen and that 2C9 Arg 108 is critical for flurbiprofen binding and changes to this residue also greatly diminish 2C9 catalyzed metabolism of diclofenac, another lipophilic anion like flurbiprofen (see entire document, in particular Results and Discussion, pages 35632-35637, including page 35634, right column, 2<sup>nd</sup> paragraph and page 35636, right column, 1<sup>st</sup> paragraph),

and

further given, as evidenced by Lewis, that substrate ingress to the p450 active site is primarily a function of substrate size, that the spatial arrangement of certain key active site residues seem to be critical for recognition and binding of particular chemical classes of substrate molecules which give rise to predictable p450-substrate interactions that can be used to accurately calculate kinetic parameters (see entire document, in particular page 2645, right column, 1<sup>st</sup> paragraph to page 2646, left column, page 2647, left column, 1<sup>st</sup> paragraph, and page 2650, right column, 1<sup>st</sup> paragraph),

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further given, as evidenced by Miners, that the single amino acid differences between the 2C9 allelic variants either have a direct effect on substrate binding and metabolism in the case of 2C9\*3 (see entire document, in particular, page 532, right columns, 2<sup>nd</sup> and 3<sup>rd</sup> paragraphs to page 533), or in the case of 2C9\*2, affect the metabolism of some, but not all p450 substrates (see entire document, in particular, page 533, left and right columns), none which would be expected by one of ordinary skill in the art to perturb the overall p450 2C9 structure,

one of ordinary skill in the art would immediately recognize that the anti-2C9\*2 antibodies of Mei would inherently "compete" with the 763-15-5 antibody and "inhibit" its binding to the 2C9 alleles as well as inhibit 2C9 catalyzed phenanthrene and diclofenac metabolism in light of the similar way in which the 2C9 p450 enzyme interacts with its substrates as evidenced by Wester and Lewis and in light of the teachings of Miners concerning the difference between the various 2C9 alleles.

Given a *prima facie* case of anticipation with a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art (see Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Patent App. & Int. 1990), it is applicant's burden to prove that the subject matter shown to be in the prior art does not possess the characteristics of the claimed invention. See In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985); In re King, 801 F.2d 1324, 1327, 231 USPQ 136, 138 (Fed. Cir. 1986). See also MPEP § 2112.

Since the Office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not compete with the 763-15-5 antibody for specific binding to the 2C9 allelic variants. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

It should be noted that claim 14 is included in this rejection because the antibodies of Mei while "cross reactive" with 2C19 according to Mei (see, in particular, page 14, 1<sup>st</sup> paragraph), do not "cross bind" 2C19 in an immunoblot (see, in particular, page 29, 2<sup>nd</sup> paragraph) and since immunoblotting requires that an antibody have an affinity of at least  $10^6 \text{ M}^{-1}$  as evidenced by Harlow at page 28, Table 3.1, the antibodies of Mei must have less than  $10^6 \text{ M}^{-1}$  affinity for 2C19 and therefore they do not specifically bind 2C19 as defined in the instant specification at page 7, 8<sup>th</sup> paragraph.

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9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 13-15, 18-22, 25, 76, 77, 80, 81 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mei et al. (WO 01/011035 A1), as evidenced by Kimura et al. (Nucleic Acids Res. 1987 Dec 10;15(23):10053-4) and the instant specification at page 2 which discloses that the 2C9\*2 allele has Cys144, and as further evidenced by Wester et al. (J. Biol. Chem. 2004 Aug 20;279(34):35630-7), Lewis et al. (Curr. Med. Chem. 2006;13(22):2645-52), Miners et al. (Br J Clin Pharmacol. 1998 Jun;45(6):525-38) and Harlow et al. (Antibodies, Cold Spring Harbor Press, pp. 23-35 (1988)), and further in view of Maeda et al. (J Med Virol. 1999 Aug;58(4):338-45).

The teachings of Mei, Kimura, the instant specification at page 2, Wester, Lewis, Miners and Harlow are given in section 7 above.

The reference teachings differ from the instant claims in that they do not explicitly recite making Fab fragments or the use of prokaryotic cells for expressing antibodies.

However, Maeda teaches antibody Fab fragments and the use of prokaryotic cells to express said fragments (see entire document, in particular Materials and Methods, pages 339-340 as well as Discussion pages 343-344, including page 344, left column, 1<sup>st</sup> paragraph). Maeda also teaches that Fab expression in prokaryotic cells is cheaper, faster and easier than Fab expression in mammalian cells (see, *ibid*).

Given the reference teachings it would have been prima facie obvious to one of ordinary skill in the art to make Fab fragments of the claimed antibodies because Fab fragments have long been known by the skilled artisan to be an alternative to full length intact antibodies, and it is obvious to substitute art recognized equivalents known for the same purpose, see MPEP § 2144.06. Moreover, the skilled artisan has long appreciated that Fab fragments often have greater ability to bind a variety of antigen sites than full length antibodies due to their small size, and therefore one of ordinary skill in the art would have been further motivated to make Fab fragments to compete with Mab 763-15-5 for 2C9 binding in that Fab could potentially compete in ways impossible for a full length competitive antibody. Furthermore, it would have been obvious to use prokaryotic cells whenever possible to express the competitive antibodies, in particular competitive Fab antibodies, since expression in prokaryotic cells is cheaper, faster and easier than in mammalian cells as taught by Maeda.

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Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

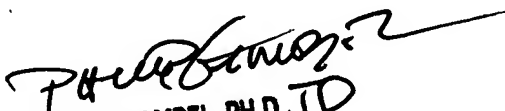
11. Claim 75 is allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Zachary Skelding, Ph.D.  
Patent Examiner  
July 19, 2007

  
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TZ 1600  
7/19/07